CLINICAL PHARMACOLOGY REVIEW

Submission	**NDA 203389/ (b) (4) S10**
Submission Date	**July 14, 2014**
Brand Name	**Procysbi®**
Generic Name	**Cysteamine Bitartrate**
Pharmacometrics Reviewer	**Jee Eun Lee, Ph.D.**
Pharmacometrics TL	**Justin Earp, Ph.D.**
Clinical Pharmacology Reviewer	**Insook Kim, Ph.D.**
Clinical Pharmacology TL	**Sue-Chih Lee, Ph.D.**
OCP Division	**DCP3/ DPM**
OND division	**DGIEP**
Applicant	**Raptor**
Formulation; Strength(s)	**25-mg and 75-mg Delayed-Release Capsules**
Proposed Indication	**Management of nephropathic cystinosis children ages 2 to 5 years**
Proposed Dosing Regimen	**1.3 g/m^2/day in two divided doses, every 12 hours. For patients who are switching from Cystagon®, (b) (4)**

1. EXECUTIVE SUMMARY

1.1. Recommendations

The Divisions of Pharmacometrics and Clinical Pharmacology 3 in the Office of Clinical Pharmacology have reviewed the information submitted in the NDA and recommend its approval for Supplement 10 with the same daily dose as that for the immediate-release formulation, Cystagon®. (b) (4)

1.2. Post-Marketing Studies

A potential PMC study is currently under discussion and detailed recommendations will be discussed in an addendum.

1.3. Summary of Clinical Pharmacology Findings

Cystagon®, immediate-release (IR) formulation, was approved in 1994 (NDA20392) as 50 mg or 150 mg capsules for oral administration. The approved maintenance dosing regimen for Cystagon is 1.3 g/m^2/day administered in 4 divided doses (Q6H), and the approved starting dose is 1/6 to 1/4 of the maintenance dose.

Procysbi® (a.k.a., RP103, cysteamine bitartrate delayed-release capsules), is a cystine-depleting agent for the treatment of cystinosis in adults and children. Procysbi was developed as delayed-release capsules for BID dosing and a 505(b)(2) application for Procysbi was approved in 2013, based on a Phase 3 non-inferiority comparison trial (RP103-03). The approved dosing regimen was the same with Cystagon (b) (4)

(b) (4)

- Supplement 10 for pediatric patients 2 to 5 years with cystinosis (b) (4)

(b) (4)

This document is a review of (b) (4) Supplement (b) (4) 10 and the review was focused on the adequacy of the proposed dose for the pediatric patients 2 to 5 years old (b) (4)

(b) (4)

(b) (4)

We recommend the use of Procysbi in the pediatric patients 2 to 5 years of age. (b) (4)

We recommend the use of equivalent dose to the approved dose of Cystagon for pediatric patients who are switching from Cystagon.

1.3.1. Baseline WBC cystine levels of newly enrolled patients were higher than those for patients who continued from Study RP103-03

The applicant proposed (b) (4)

In contrast with Study RP103-03, pediatric 2 to 5 years and transplanted patients who were newly enrolled in Study RP103-04 were not stabilized prior to the initiation of Procysbi dosing in the same way that was done in study RP103-03. The enrollment criteria for Study RP103-04 was different from those for Study RP103-03: Patients were to be on a stable dose of Cystagon® maintaining WBC cystine below 2.0 nmol ½ cystine/mg protein for Study RP103-03 but this cutoff of WBC cystine level was removed from the protocol for Study RP103-04. Therefore, a substantial portion of newly enrolled patients had WBC cystine levels above 2 nmol ½ cystine/mg protein (Figure 1 and Table 11), which undermines the adequacy of comparison of Cystagon dose and Procysbi dose for management of WBC cystine.

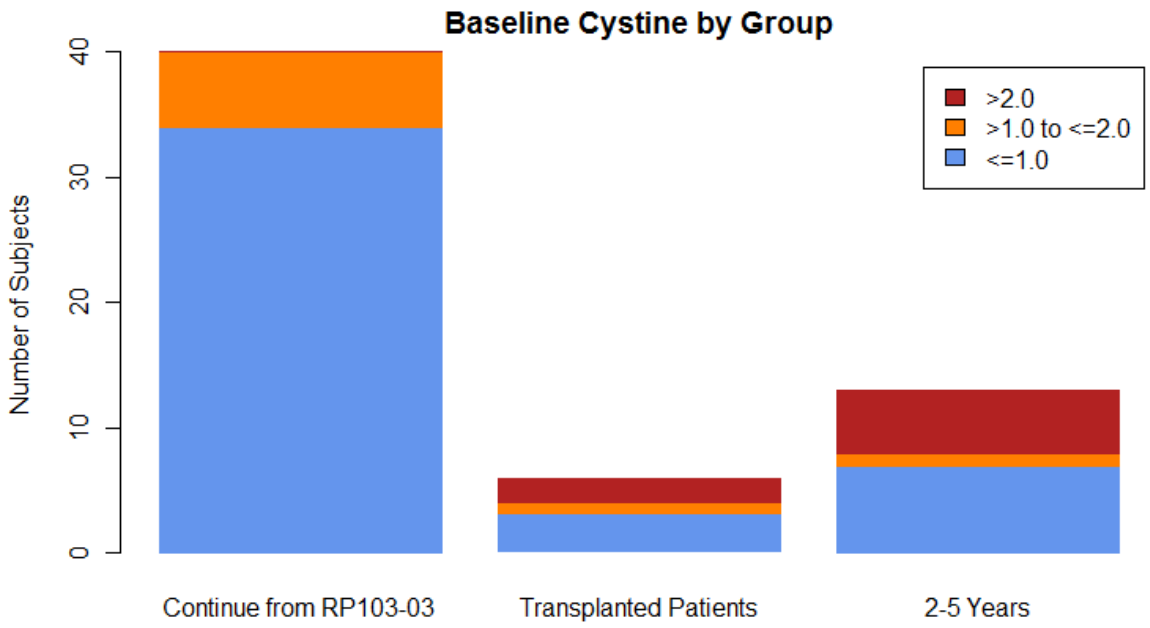


Figure 1. Distribution of baseline cystine levels by group of patients in RP103-04 (Both transplanted patients and 2-5 years were newly enrolled)
(*Source: Reviewer's analysis*)

As shown in Figure 1 and Table 11, the majority (85%) of patients who were continuing from Study RP103-03 had WBC cystine level below 1 nmol ½ cystine/mg protein and none of those had WBC cystine level above 2 nmol ½ cystine/mg protein as protocol specified as an exclusion criterion. However, 46 percent of patients 2 to 5 years of age had WBC cystine level above 1 nmol ½ Cystine /mg protein, and yet doses for those patients were not adequately adjusted (See Section 1.3.2.)

The newly enrolled patients did not undergo a Run-in period with Cystagon Q6H dosing, which was included in RP103-03 for 2 to 3 weeks. During the maximum of 28-day screening period, patients were supposed to be on a stable dose of Cystagon. However, the 'stable dose of Cystagon' was not truly a stable dose since it did not necessary maintain the WBC cystine level below 2 nmol ½ cystine/mg protein. Inclusion criteria for Study RP103-03 included this criterion clearly but it was removed from the inclusion criteria for Study RP103-04. Nonetheless, higher baseline WBC cystine levels in pediatric patients 2 to 5 years old indicated that they were not on a stable dose of Cystagon.

1.3.2. Starting doses were lower and baseline WBC cystine levels were higher for newly enrolled patients compared to those for patients who continued from Study RP103-03

For newly enrolled patients (pediatric and transplant), the dose of Cystagon prior to initiation of Procysbi dosing and the maintenance doses of Procysbi during the trial were substantially lower than those in patients who were continuing from Study RP103-03. The start dose of Procysbi for the patients who were continuing from Study RP103-03 (b) (4) of Cystagon end dose in the previous study. The start dose for these patients was the stable dose from Study RP103-03 that maintained their WBC

cysteine less than 1.0 nmol ½ cystine/mg protein. Therefore, the profiles of WBC cystine levels were different between newly-enrolled and continuing patients. As shown in Figure 2, patients who were continuing from Study RP103-03 were on stable dose of either Cystagon or Procysbi prior to Screening and the Procysbi dose was overall above 1.3 g/m^2/day maintain WBC cystine level below 1 nmol ½ cystine/mg protein. However, newly enrolled pediatric patients started Procysbi dosing at higher WBC cystine level but Procysbi dose was not adequately increased up to the cut-off time point for the interim analyses. Therefore, we cannot agree with the applicant that WBC cystine levels were well maintained with reduced dose of Procysbi in the newly-enrolled patients.

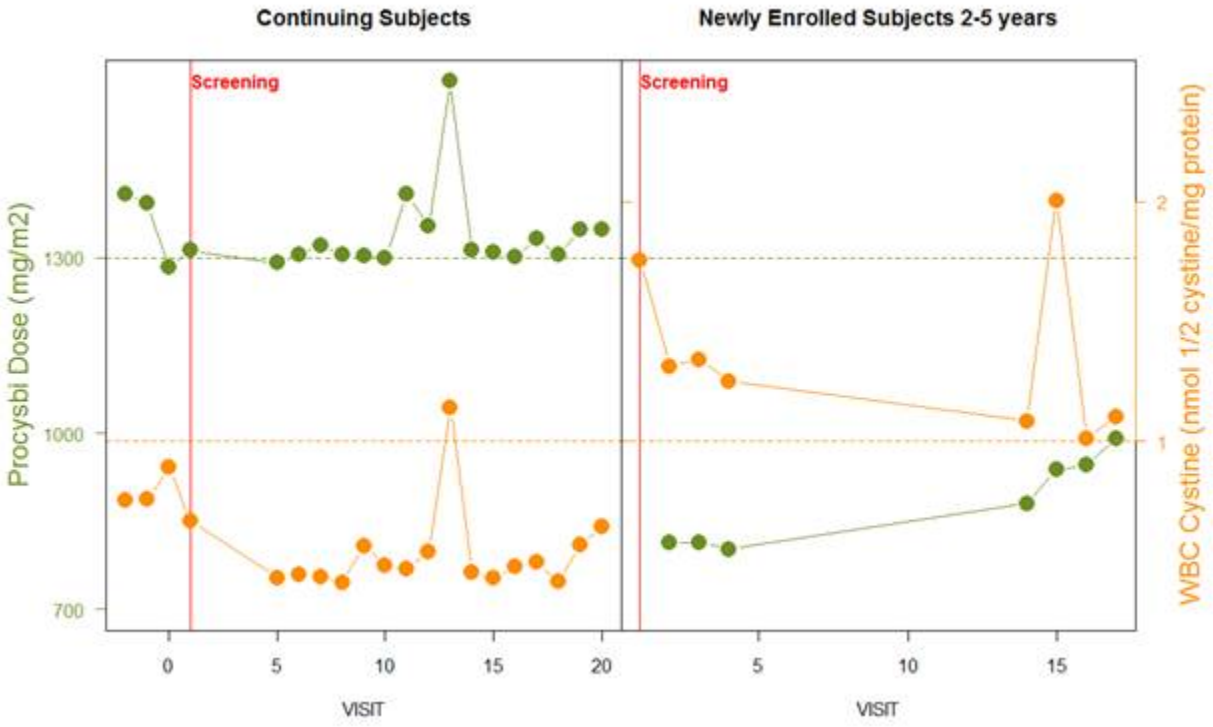


Figure 2. Mean profiles of Procysbi dose and WBC cystine levels between continuing patients from Study RP103-03 and newly enrolled pediatric patients 2 to 5 years of age. Procysbi doses are in green and their ticks are on the left side y-axis. WBC cystine levels are in yellow and their ticks are on the right side y-axis.
(Source: Reviewer's analysis)

1.3.3. The Dose-Response in pediatric patients 2 to 5 years of age supports the same maintenance dose of Procysbi with Cystagon

The dose-response relationship between daily dose of Procysbi and WBC cystine level provides evidence that the maintenance dose of Procysbi should be above 1.3 g/m^2/day to achieve the desirable PD response (<1 nmol ½ cystine/mg protein) (Figure 3). Considering that the approved maintenance dose of Cystagon is 1.3 g/m^2/day which can be adjusted to up to 1.95 g/m^2/day, (b) (4)

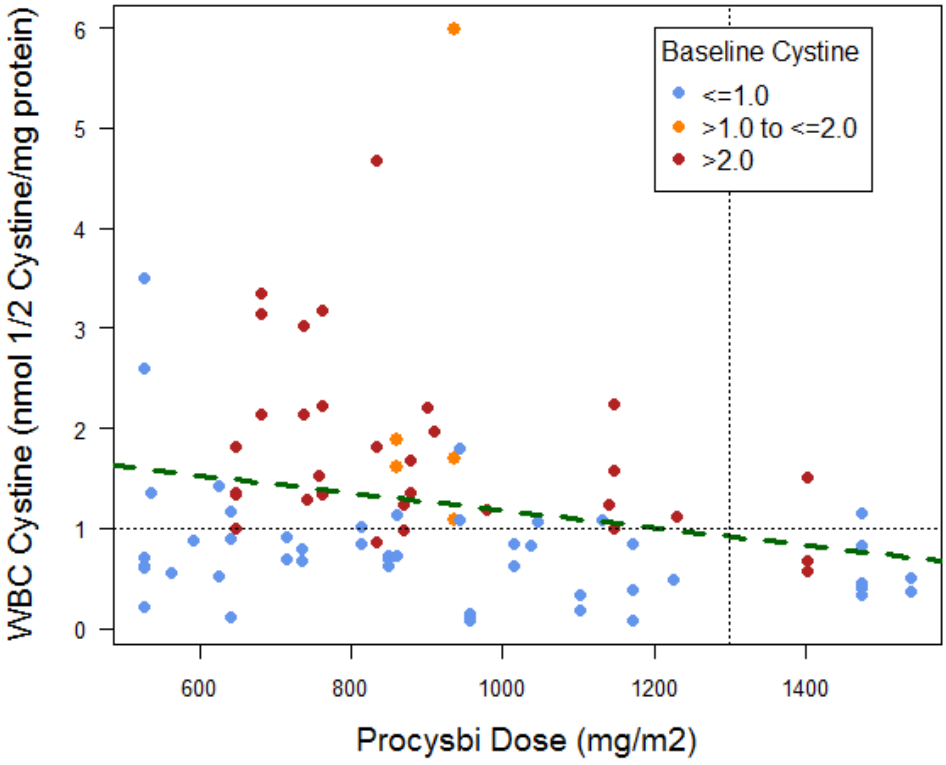


Figure 3. Procysbi dose versus WBC cystine level 30 minutes post-dose in pediatric patients 2 -5 years old.
(*Source: Reviewer's analysis*)

Furthermore, the newly added data did not change the relationship between the Procysbi dose relative to Cystagon and WBC cystine response with Procysbi® relative to that with Cystagon (Figure 4). To be able to manage WBC cystine level close to the level managed with Cystagon (horizontal line with y-value 1), the average Procysbi® should be above 91% of the Cystagon dose (regression line crosses with horizontal line at 0.91), even with these newly enrolled patients who did not appear to have received adequate dose for management of WBC cystine level.

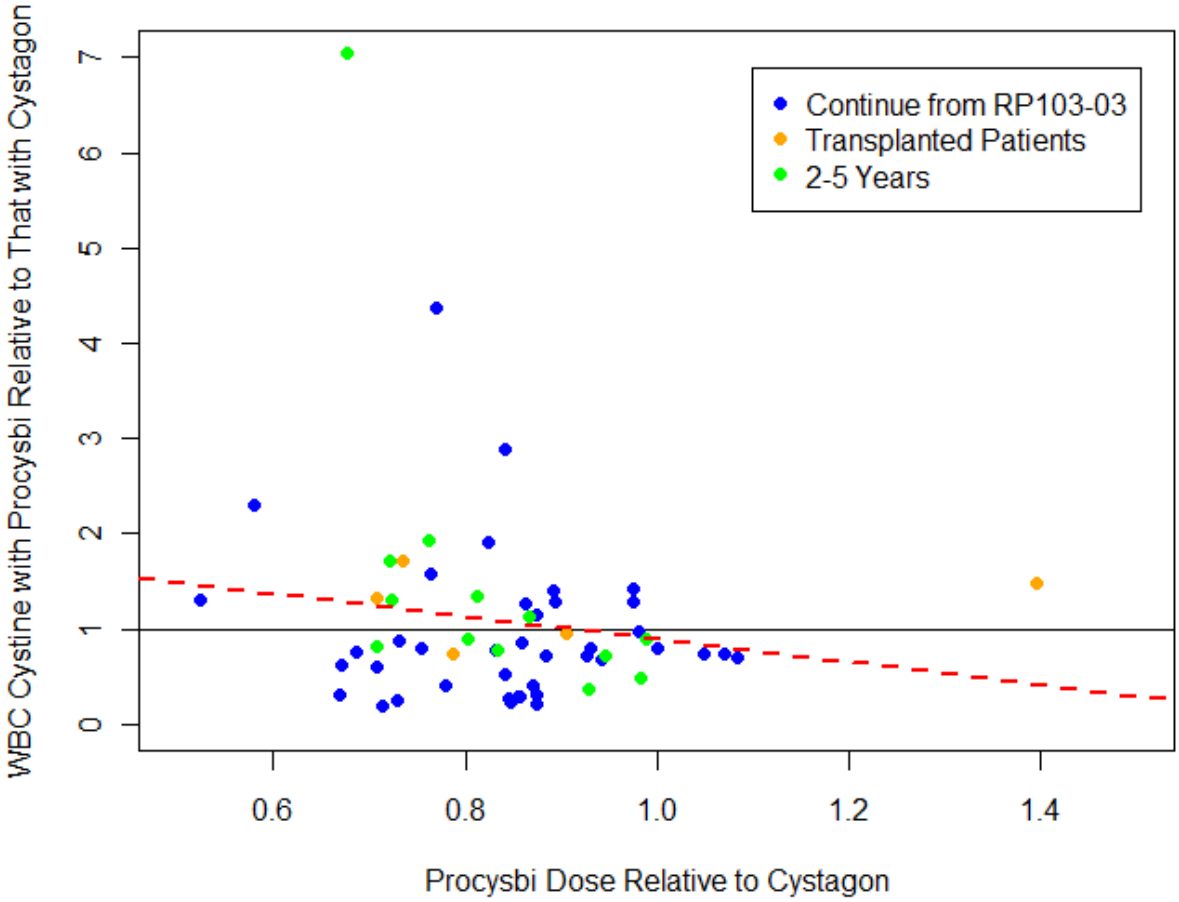


Figure 4. WBC cystine level with Procysbi relative to that with Cystagon versus dose of Procysbi relative to Cystagon (*Source: Reviewer's reproduction of the applicant's analysis*)

1.3.4. Administration instruction for Procysbi as whole capsules

Procysbi is a hard gelatin capsule containing enteric-coated (b) (4) In clinical trials, Procysbi was administered with acidic beverage such as orange juice by most patients with a few exceptions per protocol to avoid premature release of cysteamine. It was noted that in clinical trial, about 50% of patients used concomitant gastric acid reducers such as proton pump inhibitors or H_2-receptor antagonists. Currently, there is no adequate information on how administration methods (i.e. whole capsule administered with water vs. with orange juice) and concomitant gastric acid reducing agents impact the pharmacokinetics of cysteamine. In addition, the effects of concomitant gastric acid reducing agents on the pharmacokinetics of cysteamine were studied after administration of whole capsule with orange juice but not with water. Therefore the study results do not inform whether concomitant gastric acid reducing agents would have any significant impact on the pharmacokinetics of cysteamine when Procysbi capsules are administered only with water. A post-marketing study to evaluate these aspects

would be helpful to determine whether Procysbi should be administered with an acidic beverage in all patients.

2. QUESTION BASED REVIEW

2.1. General Attributes

2.1.1. What is the relevant background information and regulatory history?

Cysteamine bitartrate is a cystine depleting agent which lowers the level of cystine in white blood cells (WBCs) in patients with cystinosis. Cystinosis is an inherited defect of lysosomal transport of cystine.

Cystagon, the immediate-release formulation of cysteamine bitartrate, was approved in 1994 for nephropathic cystinosis in both children and adults. The approved dosing regimen for Cystagon consists of: a starting dose of 1/6 to 1/4 of the maintenance dose which is gradually increased over 4 to 6 weeks to the suggested maintenance dose of 1.3 g/m2/day, in 4 divided doses every 6 hours which can be increased up to 1.95 g/m^2/day to control the WBC cystine levels.

A 505(b)(2) application for Procysbi, the delayed-release formulation (RP103), was approved in April 2013 based on data from Study RP103-03, a Phase 3 study where non-inferiority of RP103 Q12H compared to Cystagon Q6H was evaluated in patients with cystinosis. Upon submission, the applicant proposed (b) (4) . Thus, the approved dose for Procysbi® remained the same as the approved dose for Cystagon. With additional data obtained from an extension trial to the Study RP103-03 (RP103-04), (b) (4) . The additional data were from newly added patients to the extension trial, consisting of two groups: pediatric patients 2 to 6 years old (N=14) and post-renal transplant patients (N=6).

2.1.2. What are the proposed indications?

The proposed indication in Supplement 10 is the management of nephropathic cystinosis in adults and children ages 2 to 5 years.

2.1.3. What are the proposed dosing regimens?

In Supplement 10, (b) (4) of the previous Cystagon dose is proposed as a starting dose of Procysbi for patients transferring from the immediate-release formulation (Cystagon). (b) (4)

2.2. What are the design features of the clinical studies to support the clinical pharmacology findings?

The applicant submitted results from interim analyses with data from Study RP103-04 which is an extension study RP103-03. Study RP103-03 was the pivotal trial supporting efficacy and safety of Procysbi in the original efficacy supplement. Detailed information about Studies RP103-03 and RP103-04 are as follows:

2.2.1. RP103-03

RP103-03 study was a randomized, crossover study in 40 subjects (male 22, female 16, mean age 12 [6-26] years excluding 2 patients whose age was < 6 years). The schematic study design for RP103-03 is show in Figure 5.

Patients were on a stable dose of Cystagon maintaining WBC cystine level below 2 nmol ½ cystine/mg protein at Screening.

A total of 43 subjects were randomized to one of two treatment sequences; 3 weeks (±3 days) treatment with Cystagon every 6 hours followed by crossover to 3 weeks (±3 days) of RP103 every 12 hours or the reverse sequence (RP103 followed by crossover to Cystagon®). Thirty nine subjects were included in the Per Protocol analysis dataset because 2 patients were discontinued and 2 patients were not compliant. All 43 subjects were included in the safety analysis.

WBC cysteine levels were measured daily for the last three days of each period and then averaged for the respective period per individual. Procysbi efficacy was determined as a non-inferiority comparison to Cystagon with a non-inferiority margin of 0.3 nmol 1/2 cystine/mg protein.

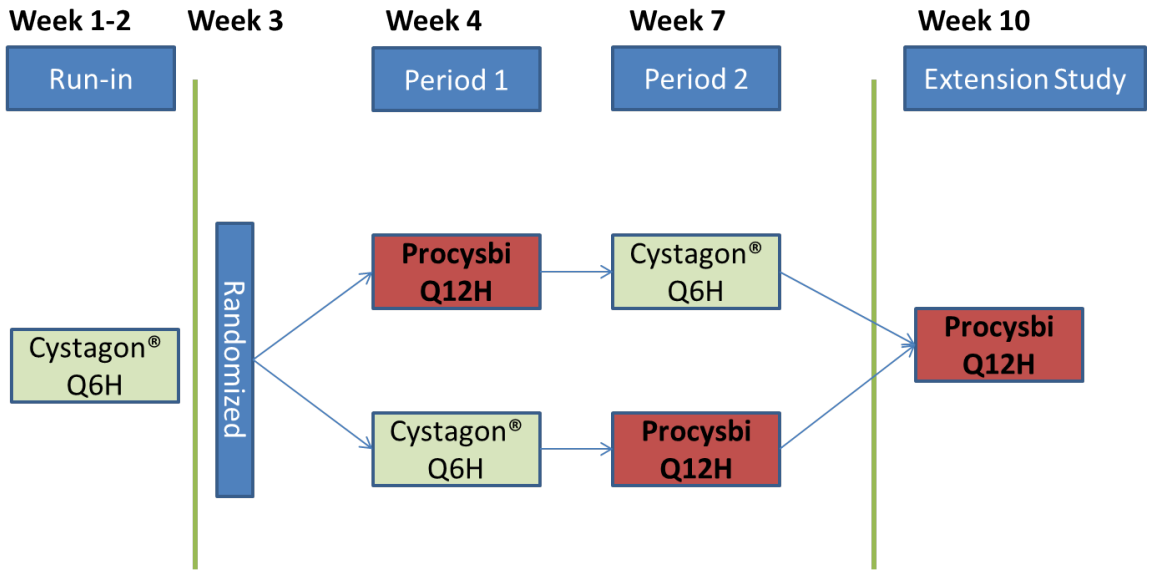


Figure 5. Schematic study design of RP103-03

Efficacy

The mean peak WBC cystine level measured in subjects treated with Cystagon was 0.44 ±0.06 nmol ½ cystine/mg protein, compared to an average peak value of 0.52 ±0.06 nmol ½ cystine/mg protein for subjects treated with RP103. The mean difference was 0.079 nmol ½ cystine/mg protein. RP103 was found to be non-inferior to Cystagon.

Safety

Incidence rates of TEAEs were 58.0% for Procysbi and 31.7% for Cystagon. Incidence rates for SAEs were 14.0% for Procysbi® and 2.4% for Cystagon and none of the SAEs were considered treatment-related.

2.2.2. RP103-04

RP103-04 study was a long-term extension study to include not only completers of the pivotal RP103-03 study (N=40), but also newly added pediatric patients 2 to 5 years of age (N=14) and transplanted patients (N=6). Unlike the Study RP103-03, WBC cystine level in the newly enrolled patients did not need to be below 2 nmol ½ cystine/mg protein, which is a critical review issue. The schematic diagram of the study is show in Figure 6.

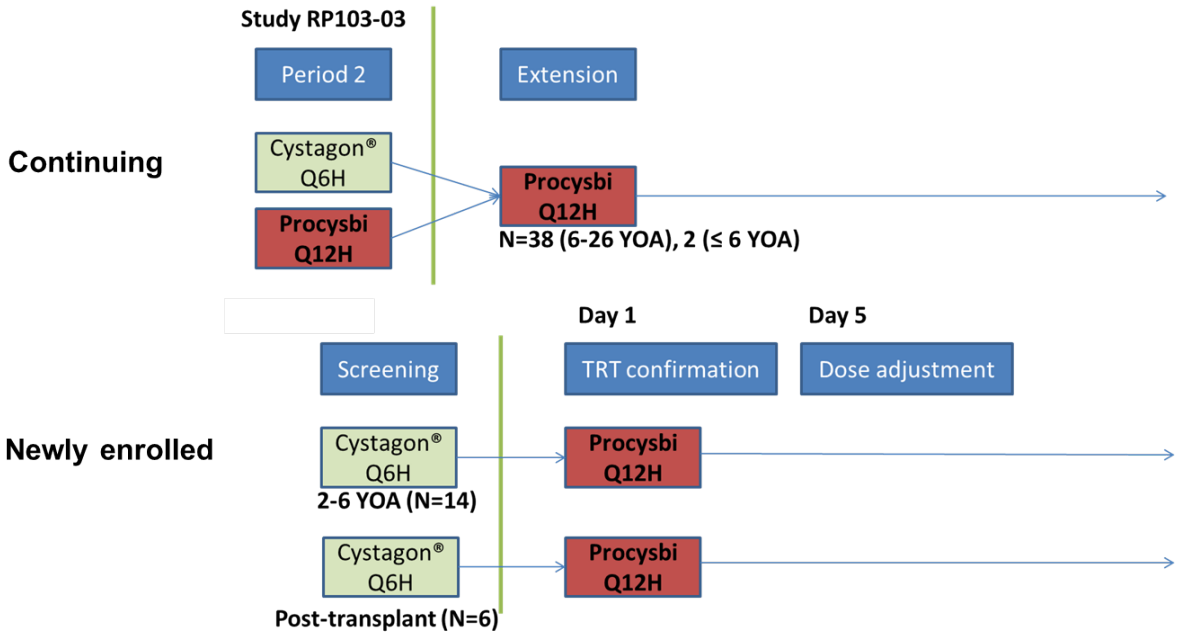


Figure 6. Schematic study design of RP103-04

Efficacy

Based on the first 6 monthly visits and the first quarterly visit, Procysbi Q12H dosing provided long term maintenance of consistent plasma cysteamine levels for the patients who continued from Study RP103-03.

(b) (4)

Safety

A total of 60 patients were enrolled in RP103-04. Forty of those previously completed RP103-04 have been treated for at least 2 years with Procysbi Q12H. Fourteen pediatric patients 2 to 5 years and 6 renal transplant patients have been treated for up to 1 and half years with Procysbi® Q12H. The incidence rate of having one or more TEAE is 56.7% for all enrolled subjects, 35.7% for pediatric patients 2 to 5 years and 33.3% for renal transplant patients. Incidence rate for GI side effects was 50% for all subjects, 21.4% for pediatric patients 2 to 5 years and 16.7% for renal transplant patients.

2.3. Exposure-Response

2.3.1. Is the exposure-response relationship similar to those observed in adults and pediatric patients with 6 years of age or older in Study RP103-03?

Yes. The range and central tendency of the response data across cysteamine exposures for pediatrics appears to superimpose with that of the adults. Additionally, pediatric patients 2 to 5 years of age appear to also require cysteamine concentration above 1 mg/L to manage WBC cystine level below 1 nmol ½ cystine/mg protein) as observed from adults and pediatric patients ≥6 years of age (Figure 7).

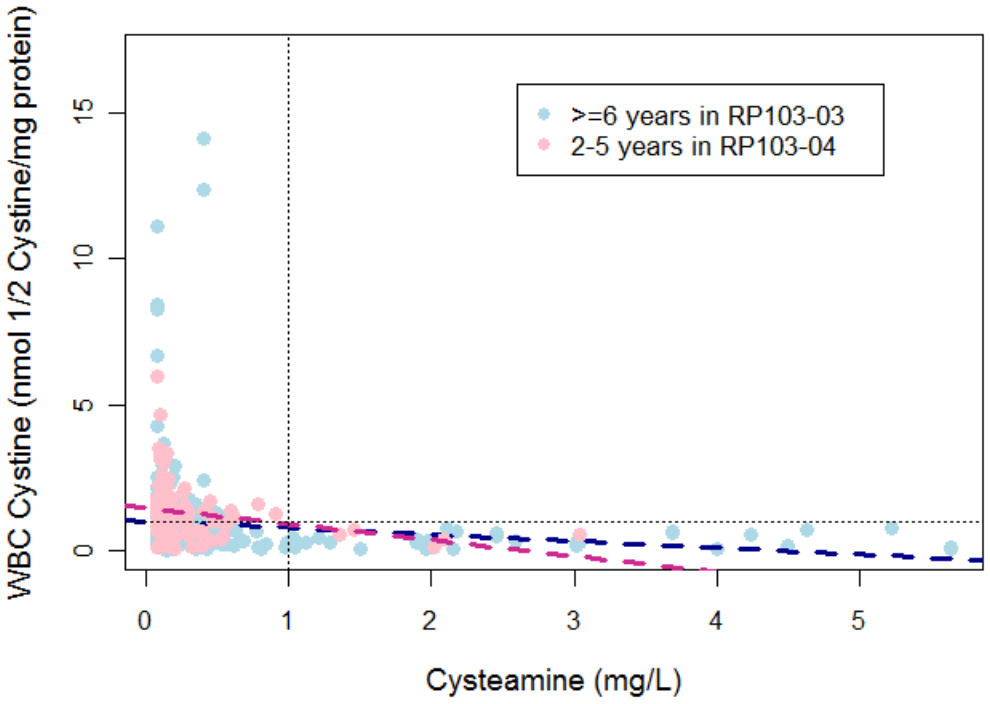


Figure 7. Exposure-response relationships in pediatric patients 2 to 5 years old in study RP103-04 and in adults and pediatrics patients ≥6 years old in study RP103-03. (Source: Reviewer's analysis)

However, the steeper linear regression line for the pediatric patients 2 to 5 years old should be interpreted with caution. The baseline cystine levels in pediatric patients 2 to 5 years old were substantially higher than those in the patients ≥6 years of age in study RP103-03. Moreover, cystine levels in the majority of pediatric patients 2 to 5 years old were not well managed (Figure 2) compared to those in the patients ≥6 years of age in study RP103-03 until the last time point available in the interim analyses. Doses of Procysbi remained sub-optimal during the study and it appears to be associated with this lower response in the pediatric patients 2 to 5 years old.

2.3.2. Is there an exposure-response relationship to support the efficacy of Procysbi in pediatric patients 2 to 5 years old

Yes. As shown in Figure 8, WBC cystine level decreases as plasma cysteamine concentration increases. This relationship is similar to that observed in adults and pediatric patients older than 6 years of age which was basis of the efficacy of Cystagon and Procysbi. Nonetheless, the concentration-response relationship indicates that the cysteamine concentration should be above 1 mg/L to manage WBC cystine level above 1 nmol ½ cystine/mg protein.

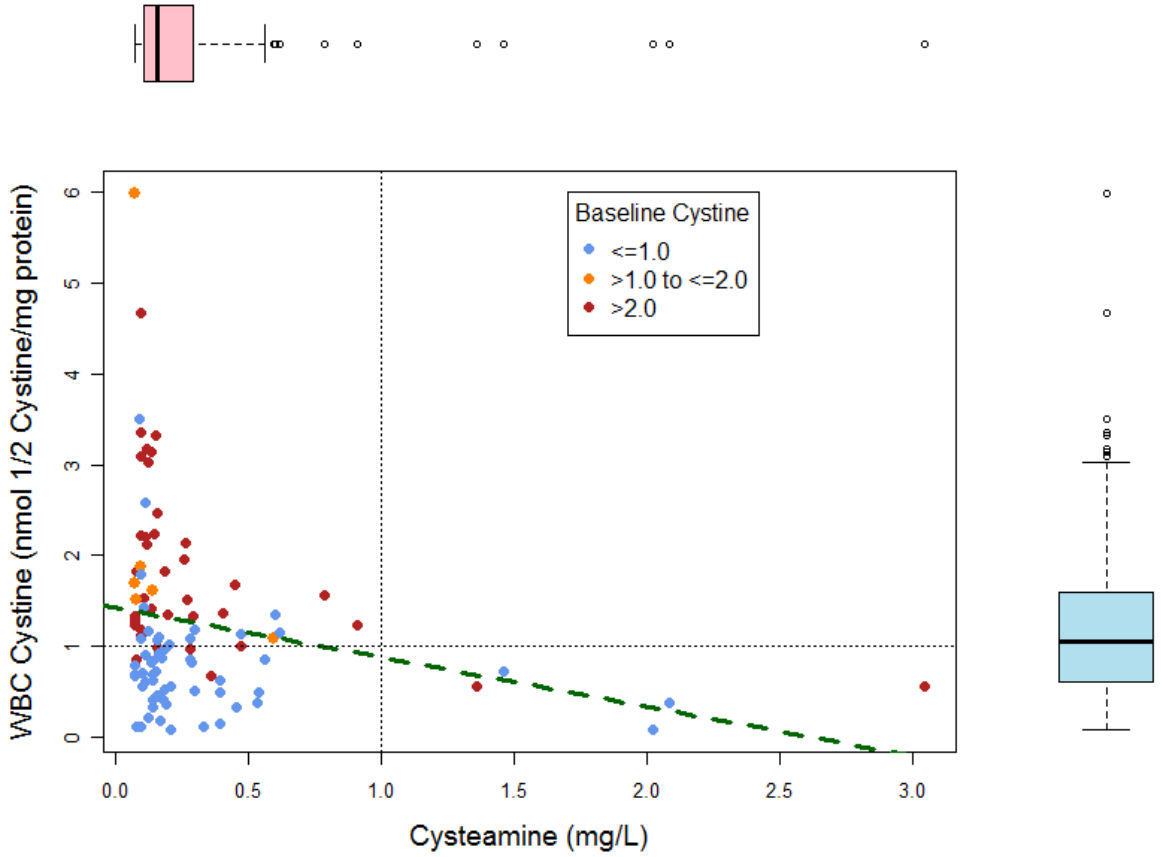


Figure 8. Plasma cysteamine concentration versus WBC cystine level. The pink boxplot above the scatter plot is for the distribution of plasma cysteamine concentrations (median 0.16 mg/mL), and the light blue boxplot on the right side is for the distribution of WBC cystine levels (median 1.05 nmol ½ Cystine/mg protein) (*Source: Reviewer's analysis*)

2.3.3. Are the studied doses and proposed dose amounts consistent with prior approved doses?

No. [redacted] (b) (4)

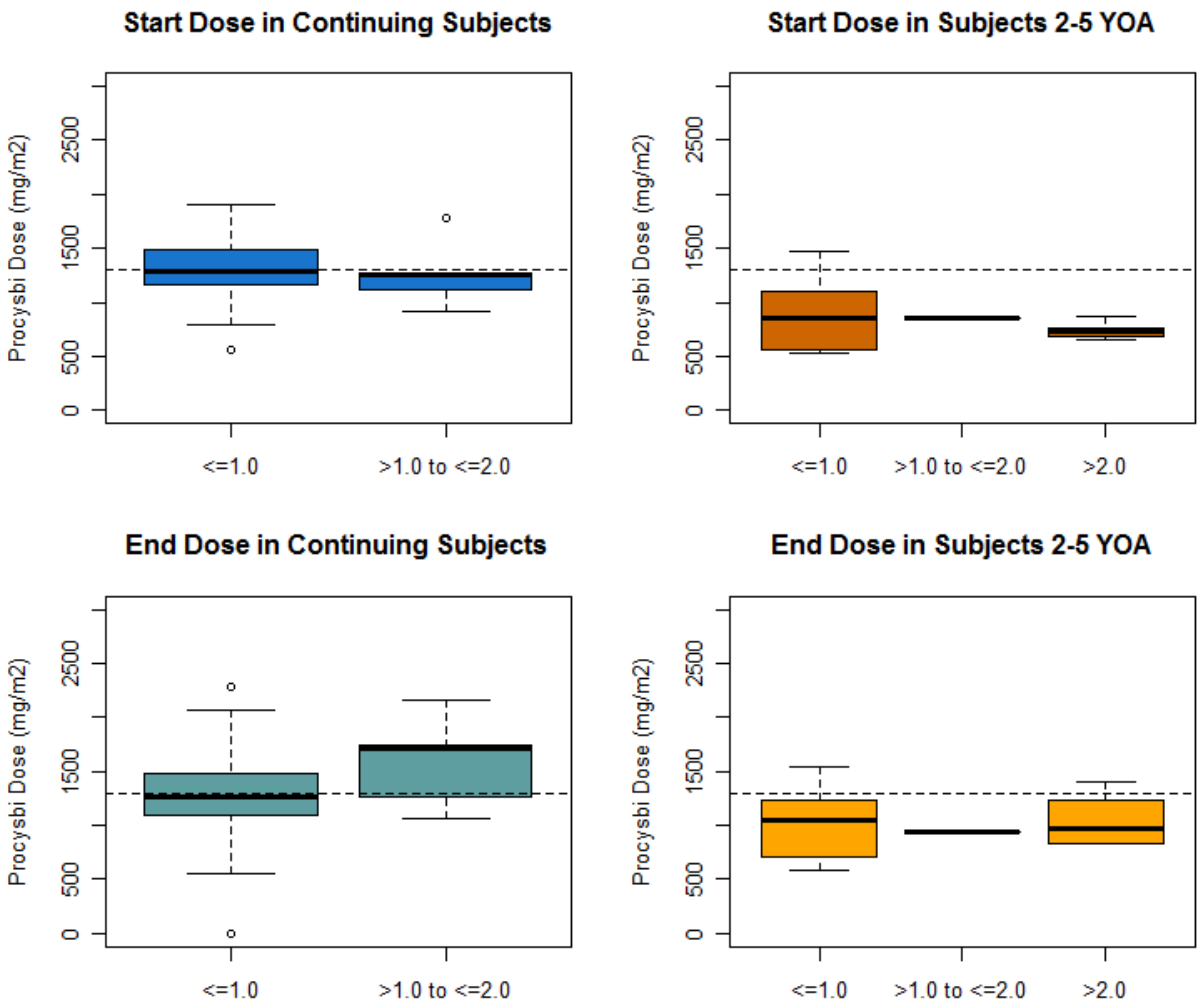


Figure 9. Procysbi dose by WBC cystine level: upper two panels for starting doses; lower two panels for end doses. (*Source: Reviewer's analysis*)

2.3.4. Is the monitoring of WBC cystine and cysteamine at 12 hours post-dose acceptable?

In this submission, the sponsor proposes to change the timing of WBC cystine and cysteamine from (b) (4) to (b) (4) to 12 hours post-dose in the labeling. The current labeling recommends WBC cystine or cysteamine monitoring at 0.5 hours post-dosing which is in consistent with the clinical trial design.

WBC cystine

The monitoring of WBC cystine concentration at 12 hours post-dose is acceptable as far as done in a consistent manner. In patients for whom WBC cystine was measured at both at 0.5 hours and 12 hours, the relationship of WBC cystine between at 0.5 hours and at 12 hours post-dose varied among patients. Out of 12 patients, WBC cystine concentration was higher at 12 hours post-dose in six patients. In three patients WBC cystine concentration at 12 hours was above 1 nmol half-cystine/mg protein when it was 0.3-0.5 nmol half-cystine/mg protein at 0.5 hours. In patients whose WBC cystine was higher at 0.5 hours than at 12 hours post-dose, WBC cystine was below 1 nmol half-cystine/mg protein at both time-points. Due to the variability among patients, it should be important that WBC cystine monitoring is performed in a consistent manner for a patient either at 0.5 hours or 12 hours post-dose.

Table 1. WBC cystine concentration after administration of Prosybi® every 12 hours in patients

	WBC Cystine (nmol half-cystine/mg protein)	
Subject #	0.5 h post-dose	12 h post-dose
2109	0.45	1.02*
2014	0.517	1.50*
9002	0.331	1.13*
8002	1.20	1.49*
3006	1.64	1.73*
6004	0.126	0.146*
1001	0.70	0.180
3008	0.618	0.521
3101	0.262	0.216
6005	0.415	0.112
7003	0.480	0.177
8001	0.743	0.440

(Source: Listing 16.2.5.8 in CSR Study RP103-03)
**Higher WBC cystine at 12 hours post-dose than at 0.5 hours post-dose*

Cysteamine

Measurement of cysteamine [redacted] (b) (4)

[redacted] (b) (4)

It should be noted that the lower limit of quantification (LLOQ) for cysteamine is 0.075 mg/L (75 ng/ml).

[redacted] (b) (4)

2.3.5. What is the effect of concomitant administration of a proton-pump inhibitor on cysteamine pharmacokinetics?

When taken with orange juice, administering 600 mg of RP103 intact capsules with the fifth consecutive daily dose of 20 mg omeprazole[1] had no significant effect on the pharmacokinetics of cysteamine in healthy subjects, as compared to administration of RP103 capsules alone with orange juice (n=20 per treatment)(Figure 10, Table 2).

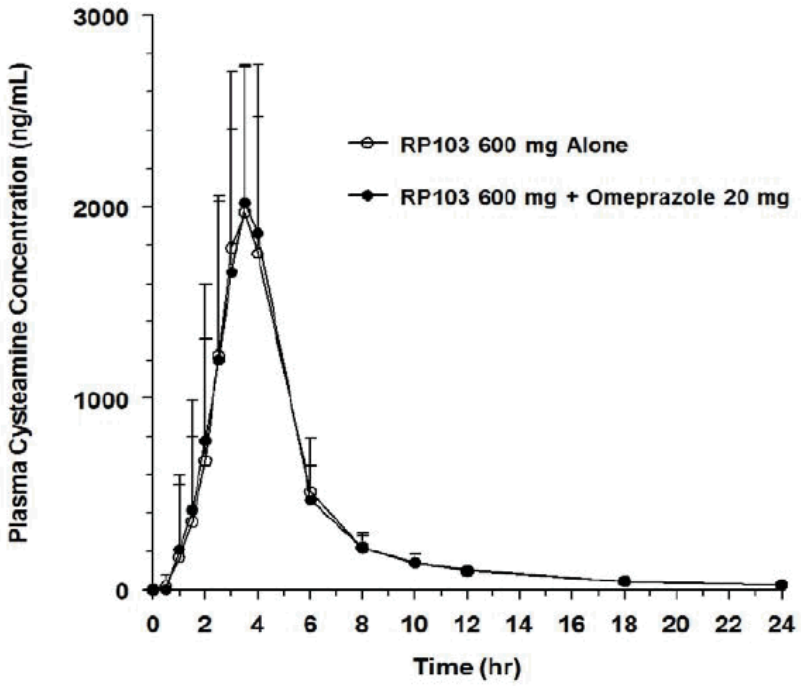


Figure 10. Arithmetic Mean (+SD) Plasma Cysteamine Concentration-Time Profiles in 20 Fasted Healthy Subjects Following a Single Oral 600 mg Dose of RP103 Capsules Given Alone and With the Fifth Consecutive Daily 20 mg Dose of Omeprazole Capsule *(Source: Study Protocol RP103-HLTA-009)*

Reviewer's comments: The application of this study result is limited because concomitant orange juice may have transiently lowered gastric pH to compound the effects of omeprazole on gastric pH. Therefore the study results do not inform whether concomitant gastric reducers would significantly affect the pharmacokinetics of cysteamine when Procysbi capsules are taken with water.

[1] The approved omeprazole is 20 mg for GERD while 40 mg is recommended for gastric ulcer.

Procysbi is a hard gelatin capsule filled with (b) (4) of cysteamine bitartrate, enteric-coated with Eudragit® that is designed to dissolve at pH (b) (4). (b) (4) (See the CMC review of original NDA 203-389 for more details). In a published study, in pediatric patients with cystinosis, cysteamine stimulates gastric acid secretion and gastrin production and a concurrent proton pump inhibitor reduced gastrin production[2]. For this reason acid-reducing agents are often used by cystinosis patients for gastrointestinal adverse events.

According to the applicant, Procysbi administration with acidic beverage was instructed to prevent potential loss of WBC cystine control due to premature release of cysteamine from formulation in case of concomitant proton pump inhibitors or meals. In clinical trial RP103-04, 58% patients took gastric acid reducing agents, mostly proton pump inhibitors at some points (Table 3). Especially among patients ≤ 6 years of age, 71% of patients (10 out of 14 patients) used a proton pump inhibitor and 14% (n=2) patients took H2-receptor antagonists (Table 4), while one (out of 6) renal transplant patient used gastric acid reducing medication i.e. H2-receptor blocker. Among patients who reported use of gastric acid reducers, 7 patients were gastric acid reducer at most of the assessment points (>50 % of the visits) while other patients use of gastric acid reducing agents appeared to be rather intermittent (Table 3).

While Procysbi was administered mostly with acidic beverage in clinical trials or in pharmacokinetics studies, two pediatric patients reported to take Procysbi with water except for the first dose. The WBC cystine concentrations in those two patients were maintained below 1 nmol half-cystine/mg protein in most of the times (Table 5). In addition, a few patients occasionally took Procysbi with water suggesting a difficulty in complying to the instruction of administration with acidic beverage. However, a formal comparison of effects of administration methods i.e. with water versus orange juice on pharmacokinetics of cysteamine after administration of Procysbi capsules was not performed (b) (4)

Table 2. Mean (SD) Plasma Cysteamine Pharmacokinetic Parameters in 20 Fasted Healthy Subjects Following a Single Oral 600 mg Dose of RP103 Capsules Given Alone and With the Fifth Consecutive Daily 20 mg Dose of Omeprazole Capsules

	Procysbi alone(n=20)	Procysbi with omeprazole(n=20)	Mean Ratio (with omeprazole/alone)(90% Confidence Interval)
Cmax (ng/ml)	2341 (608)	2454 (637)	1.04 (0.95-1.14)
Tmax (hr)a	3.5 (1-4)	3.5 (1-4)	--
AUC(0-inf) (ng*h/ml)	7607 (1924)	7708 (1621)	1.02 (0.98 -1.06)
T1/2 (hr)	5.82 (0.66)	5.67 (0.49)	--

[a]Median (range)

[2] Dohil et al. (2005) Esomeprazole therapy for gastric acid hypersecretion in children with cystinosis. Pediatr. Nephrol, 20:1786-1793

Table 3. Summary of Gastric Acid Reducing Medication Usage (Safety Population)

Medication Class/ Standard Medication Name	Safety Population All Enrolled Subjects (N=60)	
	Subject Use of GAR Medications	Episodes of GAR Medication Usage
Overall	35 (58.3)	93
Proton Pump Inhibitors (PPIs)	31 (51.7)	62
Omeprazole	15 (25.0)	24
Lansoprazole	12 (20.0)	19
Esomeprazole	3 (5.0)	11
Esomeprazole Magnesium	3 (5.0)	4
Pantoprazole Sodium	1 (1.7)	3
Pantoprazole	1 (1.7)	1
H2-Receptor Antagonists	8 (13.3)	17
Famotidine	3 (5.0)	8
Ranitidine	3 (5.0)	5
Ranitidine Hydrochloride	3 (5.0)	3
Nizatidine	1 (1.7)	1
Other Drugs for Peptic Ulcer and GERD	4 (6.7)	5
Not coded	3 (5.0)	4
Bismuth subsalicylate	1 (1.7)	1
Propulsives	3 (5.0)	4
Metoclopramide	3 (5.0)	4
Other Antiemetics	2 (3.3)	3
Dimenhydrinate	2 (3.3)	3
Aerotonin (5HT3) Antagonists	1 (1.7)	2
Ondansetron	1 (1.7)	2

Note: At each level of subject summarization, a subject is counted once if he/she reported one or more GAR medications.
Source: Table 14.3.1.9 and Table 14.3.1.11

Table 4. Summary of Gastric Acid Reducing Medication Usage (Subjects <6 Years of Age; Safety Population)

Medication Class/ Standard Medication Name	Safety Population Previously Completed RP103-03 Study (N=14)	
	Subject Use of GAR Medications	Episodes of GAR Medication Usage
Overall	11 (78.6)	27
Proton Pump Inhibitors (PPIs)	10 (71.4)	21
Lansoprazole	8 (57.1)	14
Esomeprazole Magnesium	3 (21.4)	4
Esomeprazole	1 (7.1)	2
Pantoprazole	1 (7.1)	1
H2-Receptor Antagonists	2 (14.3)	4
Ranitidine	1 (7.1)	3
Nizatidine	1 (7.1)	1
Other Drugs for Peptic Ulcer and GERD	1 (7.1)	2
Not coded	1 (7.1)	2

Note: At each level of subject summarization, a subject is counted once if he/she reported one or more GAR medications.
Source: Table 14.3.1.9b and Table 14.3.1.11b

Table 5. WBC cystine level at 30 min post-dose in pediatric patients who reported to take Procysbi with water

Days from treatment initiation	03-03-007 (male, 6.5 year old) nmol half-cystine/mg protein	03-03-008 (female 6.5 year old) nmol half-cystine/mg protein
1	0.960*	0.618*
43	0.609	0.769
84	0.514	0.617
114	0.498	0.800
149	0.552	0.502
189	0.584	1.780
208	0.357	0.236
292	0.573	0.569
392	0.480	0.571
471	0.392	0.071
593	1.330	0.775
666	0.288	0.042*

* Procysbi was administered with acidic beverage

2.6 Analytical Section

2.6.1 How was the cysteamine concentration measured in the plasma in the clinical pharmacology studies?

Cysteamine in human plasma was measured by a validated LC/MS/MS. Cysteamine was extracted from sodium heparinized human plasma by a protein precipitation extraction with acetonitrile. Before the extraction, 2-aminoethane-d4 thiol was as an internal standard, and Tris(2-carboxyethyl)phosphine hydrochloride was added as a reducing agent. A supernatant was transferred to a new plate, and diluted with mobile phase. The sample was analyzed by an LC-MS/MS system with an ammonium formate / acetonitrile/water mobile phase. The range of the standard curve was 75 - 10,000 ng/mL and was appropriate for the clinical trials.

Reviewer's comment: *The sponsor submitted an addendum to the bioanalytical method validation report for cysteamine in January 2015 in response to the Agency's request to update the duration of long-term stability of cysteamine in matrix at -80 ºC to 480 days and to 29 days for the samples with co-administered omeprazole. The samples were analyzed within the established stability period.*

Bioanalytical Sample analysis report for Study RP103-04 ((b) (4) Report # 1085-10392-002) entitled "Determination of cystine and total protein in human white blood cell lysate, and cysteamine in human plasma samples from clinical study RP103-04" was submitted.

2.6.2 How cystine and total protein in human white blood cell lysate were measured?

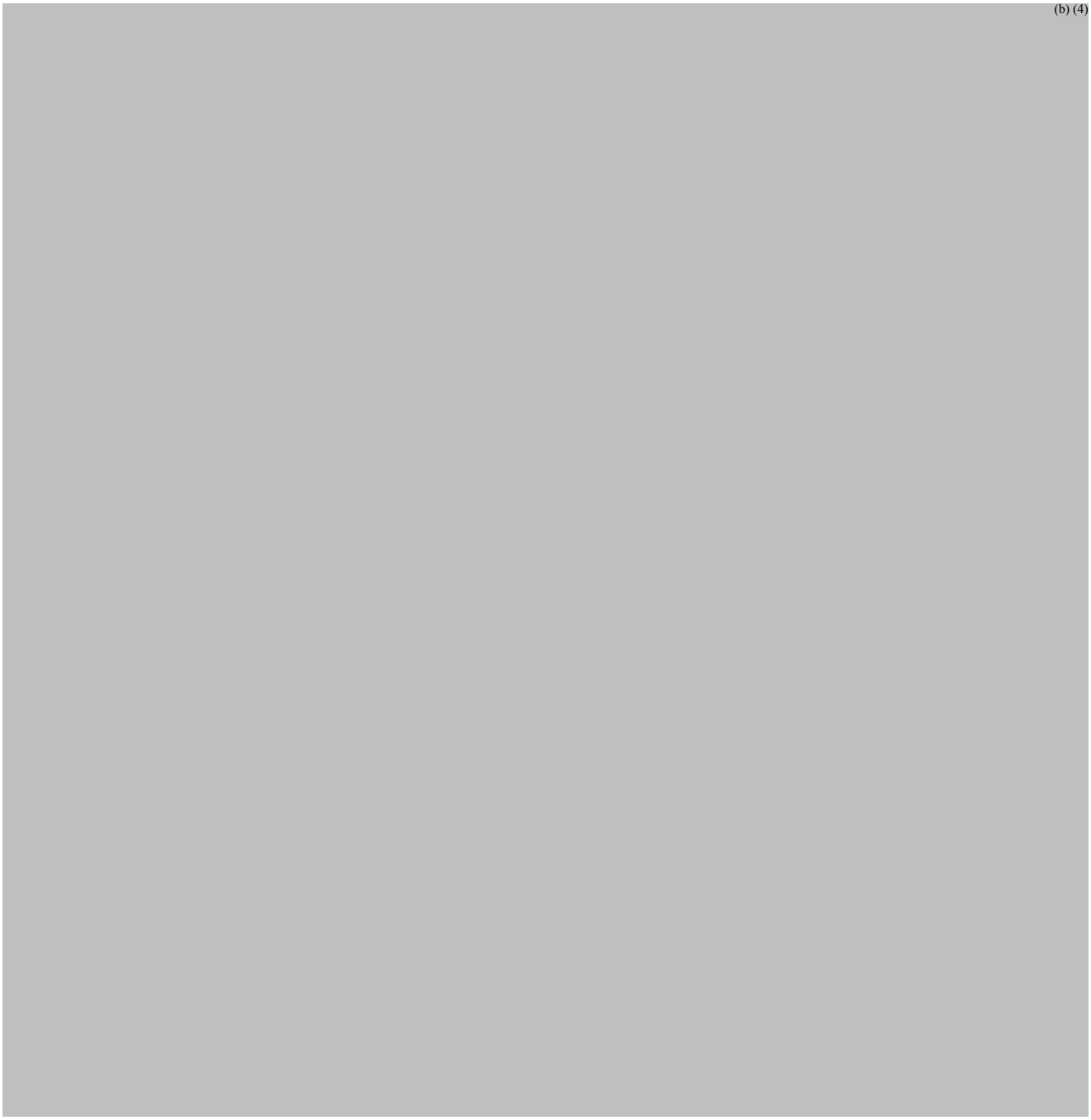
The majority of patients who completed Study RP103-03 enrolled in Study RP103-04. The same assay methods for cystine and total protein were used for Study RP103-04 and Study RP103-03.

The comparison of data from this clinical trial with historical data obtained with different assay methods or from different laboratories should be cautioned as the reference range/target concentration can vary by assay methods and between laboratories.

Cystine in white blood cell lysate

Cystine in white blood cell lysate was measured by a validated LC-MS/MS with **cystine** as a reference standard and DL-cystine-3, 3, 3', 3'-d4 as an internal standard. Cystine was quantitated from human WBC lysate by mixing the supernatant obtained after centrifugation with isotope-labeled cystine as an internal standard. The mixture was injected into an LC-MS/MS system using a SIELC Primesep 200 column with an ammonium formate/acetonitrile mobile phase. The method was initially validated for a range of 4.00- 1500 ng/mL. The samples were then treated with sulfosalicylic acid to generate a final concentration of 3 to 1130 ng/ml.

Table 6. Summary of Assay Validation for Cystine



Reviewer's comments: The cystine concentration was presented in unit of nmol half-cystine although cystine concentration was measured in the trial. The cystine concentrations measured by a tandem mass spectrometry were multiplied by 2 to be converted to concentrations of half-cystine (two cysteine

molecules form cystine). With new assay method such as tandem mass-spectrometry, cystine concentrations can be reported as it is[3],[4].

Nevertheless in practice the WBC cystine concentrations are commonly presented in unit of half-cystine because cystine in WBC lysate has been historically measured as cysteine after reduction of cystine to cysteine [5][6] and the target WBC cystine concentration i.e. 1 nmol half-cystine/mg protein has been used for cysteamine treatment monitoring[7]**Error! Bookmark not defined.**. Of note while 1 nmol half-cystine/mg protein is commonly accepted as a target WBC cystine concentration to go below, no specific assay methods are recommended by the treatment guideline.

Total protein content

The total protein content in WBC lysate was measured by bicinchoninic acid (BCA) protein assay with bovine serum albumin as a standard using commercially available assay kit (Total Protein Kit by Pierce.) The final step of sample collection at the clinical facility was acidification to precipitate the proteins. To analyze the samples for total protein the samples were centrifuged to obtain a protein (b) (4) the supernatant decanted and retained, then 0.1N NaOH is added to the (b) (4) to dissolve the proteins. The total protein concentration was indicated by a color change of the sample solution from green to purple in proportion to protein concentration, which was quantitated with reference to bovine serum albumin calibrators by monitoring the absorbance at 562 nm.

Sample analysis for RP103-04 study was initiated in the (b) (4) location in January 2011 until April 2012. All samples were then transferred to the (b) (4) location. The sponsor submitted a validation report # 1004-101507-1 in support of method (SAP.1507) transfer from one laboratory to another as the assay results were used in a longitudinal analysis. The bioanalytical assay sites were inspected and found acceptable during the original review cycle[8].

Table 7 Validation Sample Performance for total protein in WBC lysate

Protein	QC 25 mcg/ml (N=36)	2000 mcg/ml (N=18)
Mean concentration (mcg/mL)	27.4	1960
%CV	6.7	1.8

[3] Levchenko et al. (2004) Comparison of cystine determination in mixed leukocytes vs polymorphonuclear leukocytes for diagnosis of cystinosis and monitoring of cysteamine therapy. Clinical Chemistry 50, (9): 1986
[4] Wilmer, M.J. et al. (2011) Cystinosis: practical tools for diagnosis and treatment, Pediatr Nephrol, 26:205-215
[5] [5] Oshima et al. (1974) Binding assays for amino acids: the utilization of a cystine binding protein from E.coli for the determination of acid-soluble cystine in small physiological samples, J. Biol. Chem,249 (19): 6033

[6] Gahl et al.,(2002) Cystinosis, N Engl J Med, 347 (2):111
[7] Emma, F., (2014) Nephropathic cystinosis: an international consensus document, Nephrol Dial Transplant, 29: iv87-iv94

[8] The Review of EIR Covering NDA 203-3859 by Dr. Chen in Office of Scientific Investigation dated 4/4/2013

% bias	109.6	98

(Source: Applicant's (b) (4) *Report # 1004-101507-1, Table 6)*

***Reviewer's comments*:**

The applicant noted consistently lower protein content with their BCA assay when the same patient samples were re-analyzed using Lowry method at a laboratory at (b) (4) As the reference WBC cystine range was established using protein content measured by Lowry method, total protein content was corrected for the difference in methods. The applicant previously compared two protein assay methods and came up with a correction factor of 1.6999[9] as the protein content ratio measured by BCA assay was about 65% of that by Lowry method when the same sample was assayed by both methods. The assay for a standard protein i.e. bovine serum albumin was generally comparable between two methods with less than 10% of bias. Therefore, the applicant attributed the observed difference to the variability of the individually prepared samples rather than differences in test methods. The reason for the inconsistency between different methods is unclear, all WBC cystine data was corrected for the difference in total protein content assay methods.

The issue of a correction factor was also reviewed during the original review cycle and found acceptable[5]. This approach would not change the overall trend of WBC cystine change over time within patients and comparison before and after switching from Cystagon to Procysbi in this development program.

However the comparison of data from this clinical trial with historical data obtained with different assay methods or from different laboratories should be cautioned without adequate cross-validation. Therefore we recommend that the assay methods for WBC cystine should be included in the labeling with languages to indicate the potential differences for reference range/target concentration by assay methods.

3. LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The sections in red are the labeling changes proposed by the Applicant. The ~~strikethrough in red~~ text indicates recommended deletion by the reviewer. The texts in blue are recommended labeling changes by the reviewer. The *italic texts* provide the labeling recommendations rational based on this clinical pharmacology review.

Proposed labeling by the applicant and labeling recommendations by this reviewer	**Labeling recommendation rationale**
(b) (4)	(b) (4)

(b) (4)

14.2 Clinical Trials with PROCYSBI

(b) (4)

(b) (4)

- We recommend that the (b) (4)

4. PHARMACOMETRICS REVIEW

4.1. Results of Applicant's Analysis

The applicant concluded that maintenance of consistent mean and median plasma cysteamine levels is providing long-term maintenance of consistent mean and median serum WBC cystine levels. Furthermore, plasma cysteamine levels in the range of 0.1 mg/L and 0.5 mg/L are correlating well with maintenance of serum WBC cystine levels below 1.0 nmol ½ cystine/mg protein, the target level for the

previously completed RP103-03 study. However, the reviewer's analysis resulted in different conclusions from the applicant's (see Section 4.2).

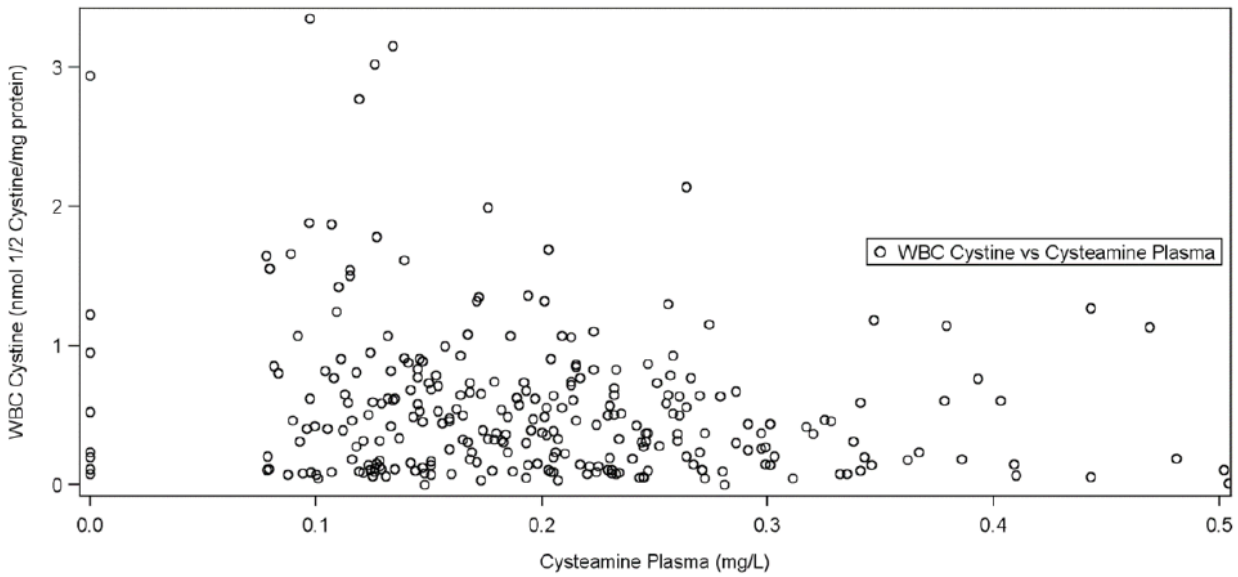


Figure 11. WBC cystine level vs. cysteamine concentration, 30 min post-dose RP103
(Source: Applicant's report, Clinical Overview, Figure 5 on page 15)

The applicant also reported analysis results for the relationship between relative WBC cystine level with Procysbi compared to Cystagon and the relative time-average daily dose of Procysbi compared to Cystagon dose (Figure 12). According to the applicant, the averages were calculated study- and treatment-wise and adjustments were made relative to the corresponding baseline measurement and taken in terms of ratios. The applicant discusses that the local polynomial regression curves for subjects who were continuing from RP103-03 and for pediatric patients 2 to 5 years, indicate good maintenance of mean dose levels. However, the adjusted cystine level and adjusted dose were not time-averaged values as the report specified. The daily measurements of cystine were adjusted by cystine level during Screening or Run-in period with Cystagon® and the daily doses of Procysbi were adjusted by Cystagon dose.

The applicant further discusses that greater bioavailability of Procysbi compared to Cystagon and better compliance of Procysbi due to its convenient Q12H dosing contributed to the need for lower dose of Procysbi® for management of WBC cystine level.

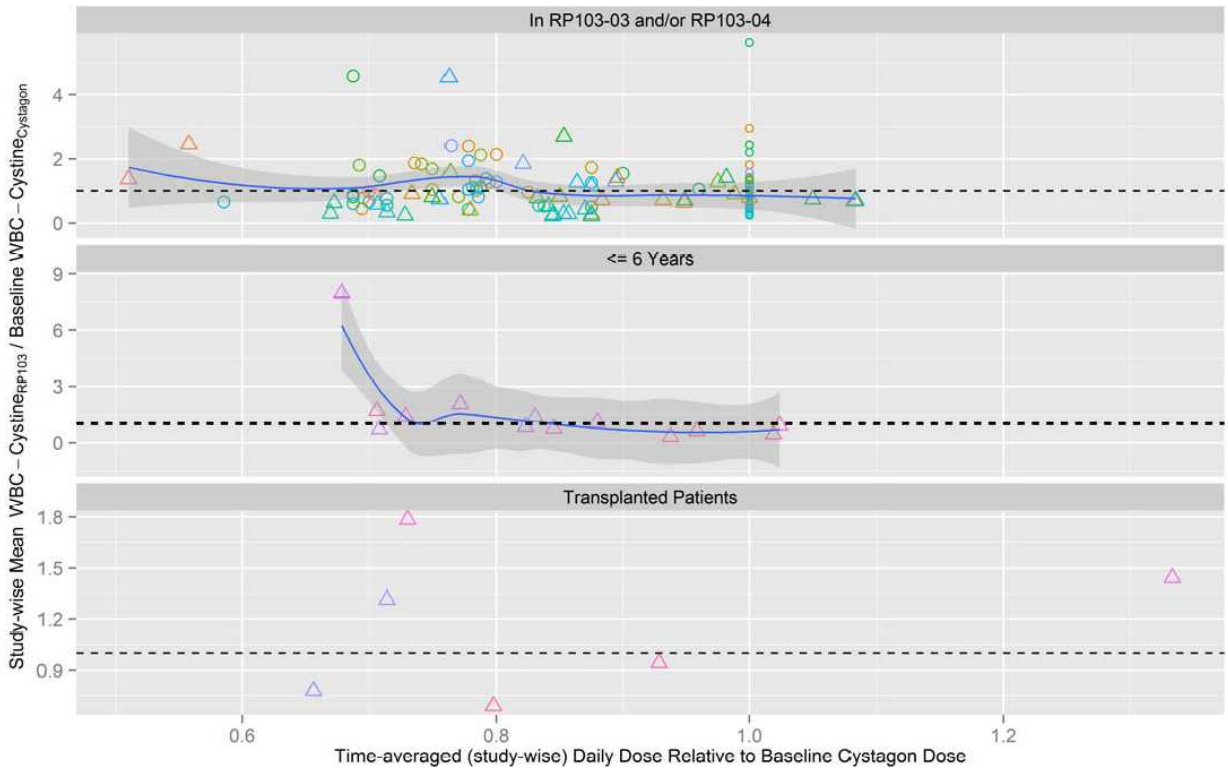


Figure 12. Adjusted WBC cystine level versus RP103 dose relative to Cystagon daily dosing.
(*Source: Applicant's report, ISE, Figure 8 on page 39)*

The starting doses in patients who were continuing from RP103-03 were higher than those who newly enrolled to RP103-04 (Table 8). The applicant did not summarize the starting doses for newly added patients in RP103-04 in a similar table for a comparison. However, larger proportion of newly enrolled patients underwent dose increase compared to those who were continuing from RP103-03 as shown in Table 9. The reviewer's analysis indicates that lower dose of Cystagon at Screening and lower start dose of Procysbi might be related.

Table 8. Summary of RP103 Starting Doses

Parameter	Safety Population Previously Completed RP103-03 Study (N=40)
RP103 Starting Dose [n (%)]	
900 to 1350 mg	15 (37.5)
1351 to 1750 mg	16 (40.0)
1751 to 2150 mg	5 (12.5)
2151 to 2600 mg	4 (10.0)
RP103 Dosing Changes [n (%)]	
Dose unchanged	13 (32.5)
Dose increased	15 (37.5)
Dosed decreased	11 (27.5)
Increases and decreases	1 (2.5)

(Source: Applicant's report, RP103-04 Interim Report, Table 12 on page 70)

Table 9. Summary of RP103 Dose Increase

	RP103-03	RP103-04		
		Continued from RP103-03 (N=40)	Transplant (N=6)	2 to 5 year (N=13)
Number with any increase from initial RP103 dosing	25 (58.1%)	18 (45.3%)	4 (66.7%)	12 (92.3%)

(Source: Applicant's report, ISE, Table 8 on page 50)

Reviewer's comments: The visual assessment of the applicant's analysis was not clearly discernable so that an optimal dose ratio of Procysbi to Cystagon could be evaluated targeting WBC cystine level accordingly. Moreover, the starting doses for the newly added patients should have been reported and compared with those who were continuing from RP103-03 for an adequate evaluation for the starting dose of Procysbi.

4.2. Reviewer's Analysis

4.2.1. Introduction

The applicant performed (b) (4)

(b) (4)

4.2.2. Objectives

(b) (4)

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

5. LISTING OF ANALYSIS CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA203389PKPD.R	PKPD modeling for efficacy	Reviews\Ongoing PM Reviews\Procysbi_NDA203389_JEL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEE E LEE
06/27/2015

INSOOK KIM
06/27/2015

SUE CHIH H LEE
06/28/2015
The NDA supplement numbers should be S-009 (not S-090) and S-010.

JUSTIN C EARP
06/29/2015